Am. J. Hum. Genet. 51:170–177, 1992

The Human Gene Encoding Acetylcholinesterase Is Located on the Long Arm of Chromosome 7

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Summary

Acetylcholinesterase (AChE) is a secreted enzyme essential for regulating cholinergic neurotransmission at neuronal and neuromuscular synapses. In view of the altered expression of AChE in some central neurological and neuromuscular disorders with a probable genetic basis, we have identified the chromosomal location of the gene encoding AChE. Chromosomal in situ suppression hybridization analysis revealed a single gene to be at 7q22, a result which was confirmed by PCR analysis of genomic DNA from a human/hamster somatic cell hybrid containing a single human chromosome 7. The AChE gene thus maps to the same region in which frequent nonrandom chromosome 7 deletions occur in leukemias of myeloid cell precursors known to express the enzyme during normal differentiation.

Introduction

Acetylcholine exhibits a protean role in cholinergic neurotransmission; functions as diverse as memory and the central control of fine motor activity are included among its known excitatory and inhibitory actions. Acetylcholinesterase (AChE) is a serine hydrolase best known for its role in terminating cholinergic nerve transmission via the esteratic cleavage of acetylcholine. The high turnover number of AChE provides for a rapid clearing of synapses of acetylcholine, enabling the postsynaptic cell to quickly recover from the initial cholinergic discharge. AChE is thus an essential component of cholinergic neurotransmission, as is evident from the full panoply of toxic symptoms arising from inhibition of this enzyme.

AChE is a secreted enzyme that undergoes extensive posttranslational modification (for reviews, see Massoulie and Toutant 1988; Taylor 1991). Addition of a variety of anchoring segments to the enzyme enables multiple forms with identical catalytic functions to be tethered to cells in discrete tissue locations. Structurally asymmetric forms containing multiple units of enzyme tetramers are found attached to the basal lamina of pre- and postsynaptic membranes, where they are anchored by disulfide linkages to a collagen-like tail unit. An additional heteromeric species consists of an amphiphilic form containing tetramers of catalytic subunits that are disulfide-linked to a hydrophobic structural subunit. Homomeric forms of AChE are represented by a soluble form and an amphiphilic form which attaches to cell membranes by a glycophospholipid moiety linked to the carboxyl terminus of the protein (Roberts et al. 1987; Silman and Futerman 1987). The latter species is the major form of AChE found in mature erythrocytes. In spite of the diverse nature of AChE molecules expressed in various tissues, molecular characterization of gene products (Gibney and Taylor 1990), cDNA clones (Schumacher et al. 1988; Sikorav et al. 1988), and genomic DNA clones (Maulet et al. 1990; Getman et al. 1991; Li et al. 1991) has revealed that a single gene encodes the AChE polypeptide in *Torpedo* and mammals. A similar conclusion was reached from genetic studies in birds (Rotundo 1988). Expression of polymorphic forms of the enzyme in various tissues is thus the result of alternative splicing of mRNA to produce multiple polypeptides containing a constant catalytic domain

Received December 13, 1991; revision received February 27, 1992.

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0002-9297/92/5101-0018$02.00

but which differ only in their carboxyl termini (Sikorav et al. 1988; Gibney and Taylor 1990; Maulet et al. 1990; Li et al. 1991).

While the essential function of AChE in coordinating cholinergic neurotransmission probably precludes the survival of individuals with an AChE gene locus mutation that interferes with expression of the protein, certain pathological conditions do feature prominent alterations of AChE expression. Notable among these is a rare autosomal recessive myasthenic syndrome characterized by an absence of the asymmetric form of AChE in neuromuscular junction endplates, along with a marked decrease in total skeletal muscle AChE activity (Engel 1990). The molecular basis for this disorder has not been elucidated. Other neuropathological disorders also show characteristic alterations in AChE distribution when ascertained by histochemistry. Examination of brain tissue from individuals with senile dementia of the Alzheimer type reveals decreased AChE activity in the hilum, dentate gyrus, fimbria, temporal neocortex, and hippocampus (Perry et al. 1980). In contrast, neurofibrillary tangles and amyloid plaques, both hallmarks of the disorder, show intense staining for the enzyme, a phenomenon which is also associated, in the basal forebrain, with degenerating axons en route to their cortical fields (Mesulam and Moran 1987; Tago et al. 1987). AChE may therefore be intimately involved in the pathology associated with Alzheimer disease. In view of the genetic basis for some forms of Alzheimer disease (Haynes et al. 1989), as well as a probable genetic linkage in certain neuromuscular disorders, we have defined the chromosomal location of the human AChE gene by fluorescence in situ suppression hybridization (FISSH) and PCR amplification of human/hamster somatic cell hybrid DNA.

Material and Methods

Hybrid Cell Lines and Cosmid Clones

Genomic DNA samples from human/hamster somatic hybrid cell lines were obtained from the Human Genetic Mutant Cell Repository (Camden, NJ). Cell line GM10791 (repository #NA10791) contains a single human chromosome 7 with the normal hamster genomic complement. Cell line GM10115 (repository #NA10115) contains human chromosome 4. Cosmid clones containing the human AChE gene were isolated from a placenta genomic library according to procedures described by Li et al. (1991).

FISSH

Preparation of metaphase chromosome spreads, biotinylation and hybridization of cosmids, and suppression reactions were performed according to methods described elsewhere (Lichter et al. 1988, 1990). Hybridized probe was visualized by treating slides with fluoresceinated avidin and biotinylated goat anti-avidin (Vector Laboratories), both at 5 μg/ml (Selleri et al. 1991). Images were produced with a laser scanning confocal microscope (Bio-Rad MRC 500). Separation of images produced by fluorescein isothiocyanate (550 mm) and propidium iodide (610 nm) fluorescence was achieved by the use of narrow bandpass filters according to a method described elsewhere (Selleri et al. 1991). Composite views encompassing both signals were then achieved by superimposing the images electronically.

PCR Amplifications

Reactions were performed with *Taq* polymerase (Perkin Elmer Cetus) in a model 50 tempcycler (Coy Laboratory Products). The sequence of the two primers used to amplify the intron region between exons 2 and 3A of AChE are as follows: HU2-3#6, 5′-**GCGAATTC**AGGCCGTGTTCACAGC-3′ (antisense); and HU2-3#7, 5′-**CGAATTC**TATGCAGGG-GCCAGCG-3′ (sense) (also see fig. 1, *top*). The nucleotides, highlighted in boldface in each primer sequence, constitute restriction-site linkers added, in previous experiments, for cloning purposes. Amplification reactions were carried out in 50-μl volumes by using 10 cycles, each consisting of denaturation at 94°C for 1 min, annealing at 49°C for 2 min, and extension at 72°C for 2 min. An additional 30 cycles of amplification then followed, each consisting of denaturation at 94°C for 1 min, annealing at 71°C for 2 min, and extension at 72°C for 2 min. An additional 7-min extension step followed the last amplification cycle. Reaction products were visualized by electrophoresing 10-μl samples of each reaction on 2% agarose gels. Products were then analyzed by Southern blotting of the gel and by hybridization with ^{32}P end-labeled oligonucleotide probe HU2-3#5 (see fig. 1, *top*).

Results

Physical mapping of genes on chromosomes is greatly facilitated by FISSH when cosmid clones labeled with biotin derivatives are used. We have used

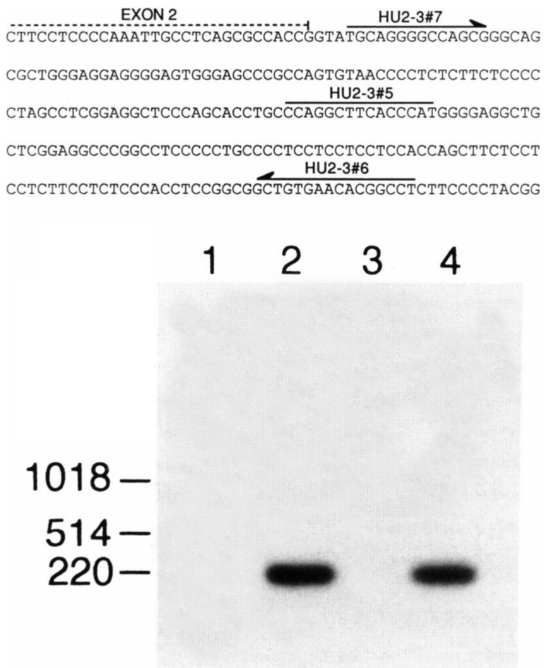

Figure 1 PCR amplification of AChE gene sequence from human/hamster somatic cell hybrid DNA. *Top,* nucleotide sequence of a portion of the intron between exon 2 and exon 3A of the AChE gene (for complete structure of the gene, see Li et al. 1991). Primers HU2-3#6 and HU2-3#7 were used for the PCR amplification. *Bottom,* Autoradiograph showing hybridization of probe HU2-3#5 to 220-bp PCR products from human genomic DNA (lane 2) and genomic DNA from a human/hamster hybrid cell line containing a single human chromosome 7 (lane 4). No amplification was observed either when DNA from a human/hamster hybrid cell line containing a single human chromosome 4 (lane 3) was used or from a reaction containing no DNA (lane 1).

FISSH to identify the location of the AChE gene on chromosome 7 in normal human metaphase chromosome spreads. Cosmid clone p18D1-1 is a pWE15 construct (Wahl et al. 1987) that contains approximately 40 kb of genomic sequence. The entire AChE coding sequence is contained within 4.8 kb of this insert (Getman et al. 1991; Li et al. 1991). This clone was labeled and hybridized to metaphase spreads made from normal human lymphocytes. The results shown in figure 2*A* clearly place the gene on the long arm of chromosome 7. Further examination of the G-type banding pattern resulting from propidium staining revealed this gene to be located in band q22 (fig. 2*B*).

To confirm this result, we used PCR to amplify the AChE gene sequence from human/hamster somatic cell genomic DNA from a hybrid cell line containing a single human chromosome 7. The primers used in this amplification, HU2-3#6 and HU2-3#7, are located within the intron between exons 2 and 3A of the AChE gene (fig. 1, *top*). The identity of the DNA sequences amplified by PCR was confirmed by Southern blotting of the PCR-amplified products onto nitrocellulose membrane, then by probing the products with a third oligonucleotide primer (HU2-3#5) located within the 2-3 intron. Use of primers HU2-3#6 and HU2-3#7 in the PCR reaction allowed the amplification of a 220-bp fragment in human genomic DNA and in somatic cell hybrid DNA containing human chromosome 7 (fig. 1, *bottom*, lanes 2 and 4, respectively). To ensure that DNA fragments produced in the PCR reaction were not of hamster origin, we also amplified genomic DNA obtained from a human/hamster somatic hybrid-cell line containing human chromosome 4. This DNA showed no amplification product on the gel, under identical reaction conditions (fig. 1, *bottom,* lane 3).

Discussion

The extensive structural diversity of AChE molecules is thought to provide a means for anchoring the enzyme in specific tissue environments. A variety of posttranscriptional and posttranslational mechanisms are known to be employed in producing this diversity (Schumacher et al. 1988; Sikorav et al. 1988), which reinforces studies using *Torpedo* (Maulet et al. 1990) and mammalian (Li et al. 1991) tissues, that identified only a single gene encoding the AChE polypeptide. The data presented here provide visible confirmation for the existence of a single gene for AChE in higher organisms, a finding which matches that from studies of the quail genes (Rotundo 1988) and the *Drosophila* AChE genes (Nagoshi and Gelbart 1987) but which differs from the three genetic loci that reportedly influence AChE activity in *Caenorhabditis elegans* (Johnson et al. 1988).

At present there is no evidence that suggests that a chromosomal abnormality in the AChE locus at 7q22 is involved in the genesis of neuropathological conditions such as Alzheimer disease, although trisomy 7 has been detected in some cell types in brain tissue both from normal individuals and from patients diagnosed with malignant gliomas (Heim et al. 1989). Figure 3 shows genes that have been found on the long arm of chromosome 7, including proα_2(I) collagen at 7q21.3 (Kere et al. 1991), laminin B1 at 7q22 (Pikkarainen

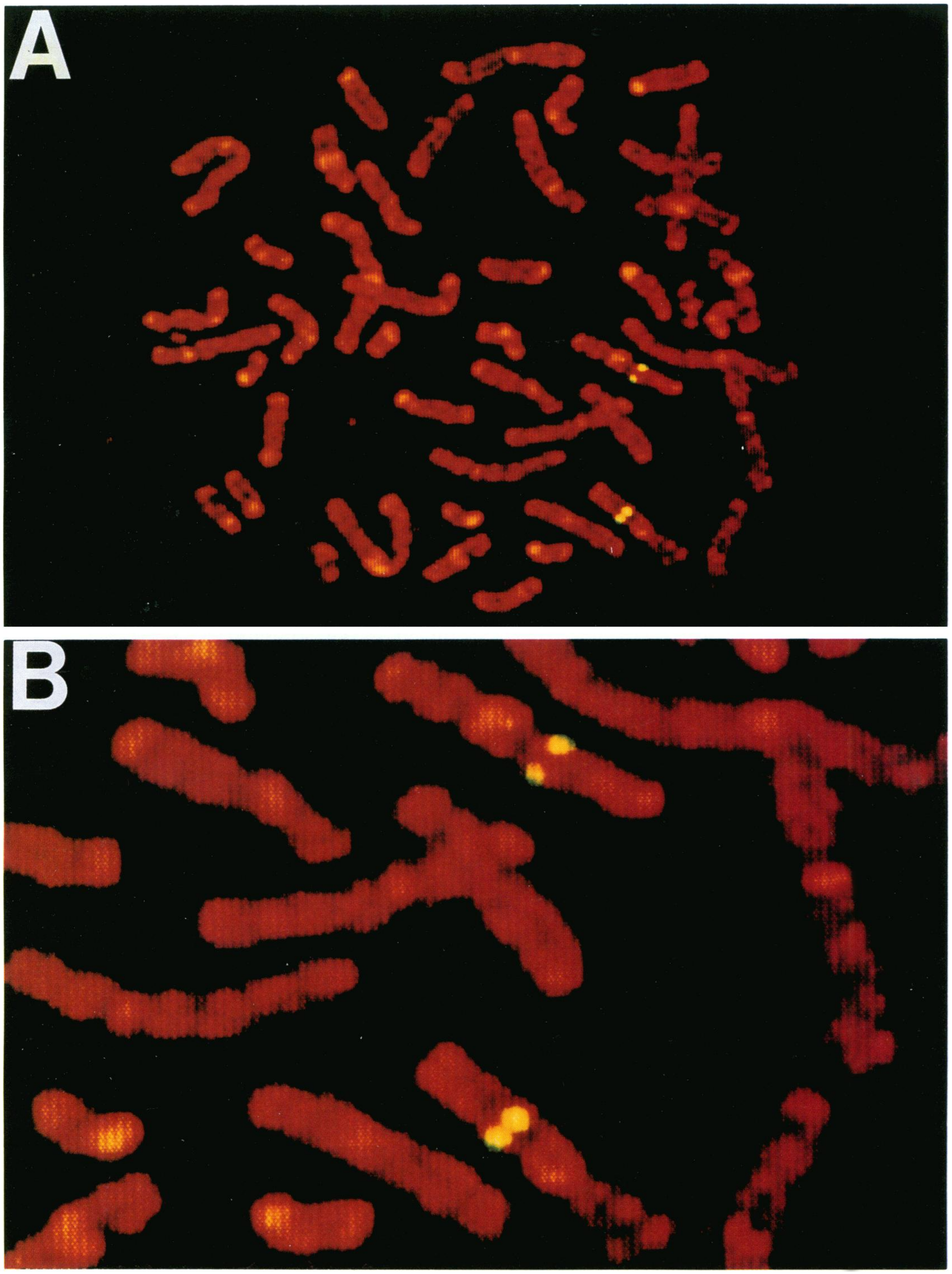

Figure 2 FISSH with cosmid DNA containing the AChE gene, to metaphase chromosomes from normal human lymphocytes. Biotinylated cosmid DNA was prepared as described by Lichter et al. (1990) and was detected by fluoresceinated avidin. Visualization of chromosomes was achieved by staining with propidium. Images were prepared by collecting data on a Bio-Rad MRC500 confocal microscope and by electronically enhancing fluorescent signals from each dye. *A,* Hybridization of AChE clone p18D1-1 to two pairs of chromosome 7 chromatids. *B,* Enlarged view, showing location of hybridized probe in the q22 region of the chromosome.

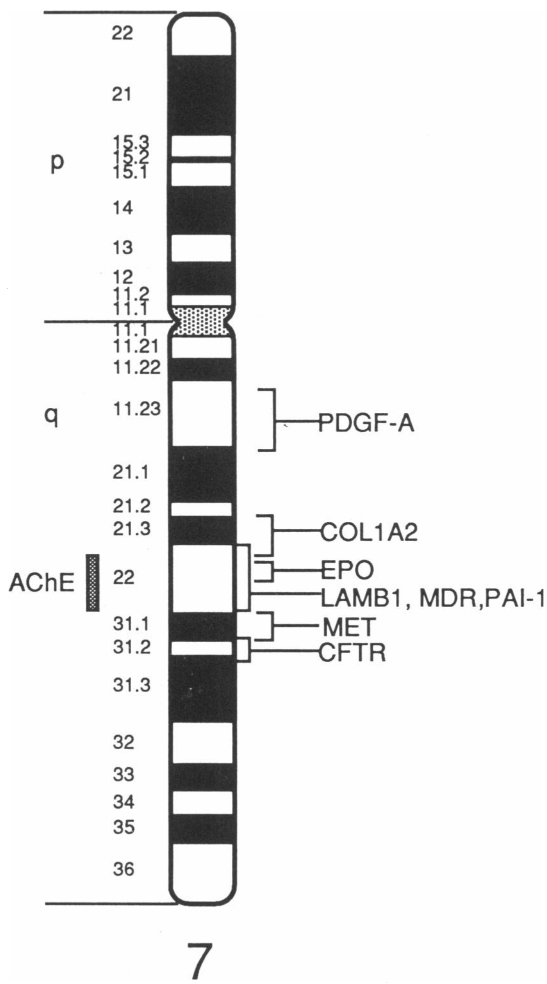

Figure 3 Ideogram of human chromosome 7, showing the physical location of the AChE gene and other genes on the long arm. EPO = erythropoietin; MDR = multi-drug resistance P-glycoprotein 1; PAI-1 = plasminogen activator inhibitor type 1; MET = c-met proto-oncogene; PDGF-A = platelet-derived growth factor A chain; COL1A2 = proα_2(1) collagen; LAMB = laminin B1; CFTR = CF transmembrane regulator.

et al. 1987), and the cystic fibrosis transmembrane regulator (CFTR) at 7q31.1-31.3 (Rommens et al. 1989; Green and Olson 1990). A number of genes expressed in hematopoietic tissues have also been localized on or near the q22 band of chromosome 7. These include genes encoding the YT blood group antigen (Zelinski et al. 1991), platelet-derived growth factor A chain, plasminogen activator inhibitor type 1, the multidrug-resistance P-glycoprotein, erythropoietin, and MET (Dean et al. 1985; Kere et al. 1991). The MET locus corresponds to the proto-oncogene c-met, a membrane-bound tyrosine kinase expressed in Hodgkin lymphoma cell lines (Jucker et al. 1990) and in many other tissues. c-met serves as the receptor for the plasminogen-related protein hepatocyte growth factor (HGF) (Buttaro et al. 1991). Like AChE, HGF is located in leukocytes and in platelets (Nakamura et al. 1987), which indicates that it is expressed in megakaryocytes. The presence of glycophospholipid-anchored forms of AChE on erythrocyte membranes (Roberts et al. 1987) and the expression of the enzyme during megakaryocyte differentiation (Burstein et al. 1985) would qualify AChE as a member of this group of hematopoiesis-related genes. However, it is possible that the apparent grouping of hematopoietic genes in this region is merely a function of the source of cloned sequences available for localization studies, since it has been estimated that 2,700 genes are located on chromosome 7 (Stephens et al. 1990).

The chromosomal location of the AChE gene may be of relevance to the expression of the enzyme in cells of the myeloid lineage, since abnormalities in chromosome 7 are a consistent nonrandom cytogenetic finding in acute nonlymphocytic leukemia (ANLL) and myelodysplastic syndromes (MDS) (Bernstein et al. 1984). These disorders are commonly found in patients who have been exposed to chemotherapy or radiation treatments and are characterized by abnormalities in differentiation and proliferation of multiple cell types of the myeloid lineage. In one retrospective study of chromosome 7 abnormalities in ANLL (Bernstein et al. 1984; Kere et al. 1987, 1989), the most common breakpoint (found in 10 of 17 patients) on the long arm of the chromosome was found to be at 7q22, which is the same region in which the AChE gene is located. A more recent review of 31 cases of histochemically diagnosed megakaryoblastic leukemia also revealed a frequent occurrence of −7/7q-chromosome abnormalities (Cuneo et al. 1989). Since the expression of AChE during megakaryocyte differentiation is considered to be phenotypic for maturation of these cells (Burstein et al. 1985), disruption of the AChE gene locus by chromosomal deletion may interfere with normal megakaryocyte maturation, leading to inappropriate proliferative growth of megakaryocyte precursors. This possibility is supported by evidence that indicates that abnormal proliferation of mouse megakaryocyte precursors can be induced, both in vivo and in vitro, by esterase inhibitors and acetylcholine analogues (Burstein et al. 1985; Patinkin et al. 1990).

The butyrylcholinesterase (BChE) and AChE genes have been found to be coamplified in peripheral blood cells of some patients with platelet disorders resulting from abnormal megakaryocytopoiesis (Lapidot-Lifson et al. 1989). It is interesting that the BChE gene has been mapped by linkage analysis and by in situ hybridization to two positions on chromosome 3 (i.e., 3q21 and 3q26) (Soreq et al. 1987; Zakut et al. 1989), a region in which chromosomal breakpoints have been found in some cases of megakaryoblastic leukemia (Cuneo et al. 1989) and in tumors of neuronal and glial origin (Berger et al. 1985). More recent fine-mapping studies have confirmed by in situ hybridization that the BChE gene is located at the 3q26.1-q26.2 region of chromosome 3 (Gaughan et al. 1991). BChE probes have also been reported to hybridize to an additional site on chromosome 16 (i.e., 16q12-24) (Zakut et al. 1989), although genomic cloning studies have determined that a single gene encodes the BChE polypeptide (Arpagaus et al. 1990). Our finding that the AChE gene is localized to chromosome 7 indicates that the multiple sites reported in BChE gene localization studies are not due to cross-hybridization of BChE probes to AChE gene sequence.

Amplification of AChE and BChE genes in patients with MDS may be the result of gene replication similar to the DNA amplification that has been reported to be associated with chromosomal breakpoints in a number of other malignancies (Bishop 1987). Future studies involving fine mapping of both loci will be required for an understanding of the relationship between esterase genes and chromosomal breakpoints in myeloid disease.

Acknowledgments

This work was supported in part by USPHS grant GM18360 and a Muscular Dystrophy Association grant (to P.T.), by a French Foundation for Alzheimer Research Fellowship (to D.K.G.), by California State Public Health contract 89-97725 (to D.K.G. and P.T.), and by grants (to G.A.E.) from the National Institutes of Health, the Department of Energy, the March of Dimes Birth Defects Foundation, and the G. Harold and Leila Y. Mathers Charitable Foundation. We thank Caryn Wagner-McPherson for cytogenetic analysis of metaphase chromosome spreads, and we thank Ying Li for helpful discussions.

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